PATENT SPECIFICATION

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Int. Cl.:—C 07 c

COMPLETE SPECIFICATION

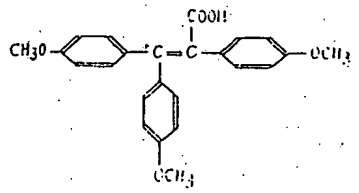
Tris-(*p*-Methoxyphenyl)Ethylene Derivatives

I, GIUSEPPE CARLO SIGURTÀ, (trading as Sigurtà Farmaceutici), of Italian Nationality, of 19, Via Canova, Milan, Italy, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention generally relates to the preparation of organic compounds possessing estrogenic activity and, more particularly, it is concerned with new and advantageous estrogenic compounds which possess the desirable property of a good tolerance without undesired side-effects. The products prepared according to the present invention may be administered orally in suitable pharmaceutical preparations, such as tablets, capsules and dragées.

According to the present invention, a method for the preparation of tris-(*p*-methoxyphenyl) ethylene derivatives possessing estrogenic properties is characterised by the esterification or reduction of tris-(*p*-methoxyphenyl) acrylic acid, or reaction of a corresponding compound, wherein the carboxyl group is replaced by a bromine atom, with an alkyl lithium and N,N-dimethyl chloroformamide, without causing modification of the three *p*-methoxyphenyl groups.

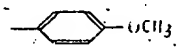
The objects and scopes of the present invention will be clearly understood by a consideration of the formula of tris-(*p*-methoxyphenyl)-acrylic acid:



(1)

containing three *p*-methoxyphenyl groups

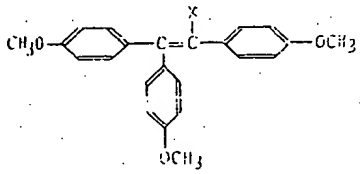
[*Price 4s. 6d.*]



(2)

which undergo no modification since the transformation which is the feature of the present invention is limited to the carboxylic function thereof.

The compounds of the present invention may be therefore represented by the general formula:



(3)

wherein X represents a carboxylic acid ester, dialkylamide or hydroxymethyl group, and wherein the three *p*-methoxyphenyl groups shown by (1), whose separated formula is (2), remain unchanged in the preparation of said compounds.

Some examples are given hereinbelow, including analysis data, to illustrate the methods whereby the compounds of the present invention may be prepared. Such examples relate to the preparation of some esters, as well as of an amide and an alcohol, which is accomplished by said transformation.

EXAMPLE 1

Tris-(*p*-methoxyphenyl)-acrylic acid methyl ester

Nitrosomethyl urea (9.1 g.) was added with stirring to 25 ml. of a 50% potassium hydroxide solution under 80 ml. of ether. The ether layer was separated, dried over solid

potassium hydroxide and decanted. To this ether solution of diazomethane, 12 g of tris-(*p*-methoxyphenyl)-acrylic acid were added while the temperature was maintained at 10°C. When nitrogen evolution had ceased, the ether and the excess of diazomethane were distilled off. Evaporation to dryness of the residue in vacuo left a yellow oil which solidified upon cooling. There was thus obtained 12.2 *g* (yield 97%) of a product melting at 100—102°C.

After recrystallization from ethanol, the melting point was 105—106°C.

Analysis:

Calculated for $C_{25}H_{24}O_5$: C 74.25 H 5.98
Found: C 74.10 H 5.95

EXAMPLE 2

Tris-(*p*-methoxyphenyl)-acrylic acid n-propyl ester

The sodium salt of the acid was first prepared by dissolving it in a stoichiometric volume of normal NaOH and evaporating the solution to dryness in vacuo. The sodium salt thus obtained (3.1 g) was dissolved in a mixture of 42.5 ml of ethanol and 7.75 ml of water; 1.33 g of n-propyl iodide were added and after the mixture had refluxed for 12 hours, it was evaporated in vacuo, extracted by ether and the ether solution washed with water and dried over dry Na_2SO_4. After removal of the ether, the residue was crystallized from ethanol. There was thus obtained 2 g of tris-(*p*-methoxyphenyl)acrylic acid n-propyl ester melting at 124°C.

Analysis:

Calculated for $C_{28}H_{30}O_5$: C 74.98 H 6.53
Found: C 74.72 H 6.38

EXAMPLE 3

Tris-(*p*-methoxyphenyl)-acrylic acid n-butyl ester

The sodium salt of the acid was first prepared by dissolving it in a stoichiometric volume of normal NaOH and evaporating the solution to dryness in vacuo. The sodium salt thus obtained (3.1 g) was dissolved in a mixture of 42.5 ml of ethanol and 7.75 ml of water; 1.46 g of n-butyl iodide were added and after the mixture had refluxed for 12 hours, it was evaporated in vacuo, extracted by ether, and the ether solution washed with water and dried over dry Na_2SO_4. After removal of the ether, the residue was crystallized from ethanol. There was thus obtained 2.2 g of tris-(*p*-methoxyphenyl)-acrylic acid n-butyl ester melting at 77°C. after several recrystallizations from a 1:4 mixture of ether and petroleum ether.

Analysis:

Calculated for $C_{29}H_{32}O_5$: C 75.31 H 6.77
Found: C 75.06 H 6.50

EXAMPLE 4

Tris-(*p*-methoxyphenyl)-acrylic acid N-dimethyl amide

To a solution of butyl lithium, prepared from 1.5 g of lithium and 12 g of N-butyl bromide in dry ether, a suspension of 21 g of tris-(*p*-methoxyphenyl)-bromoethylene in 300 ml of dry ether was added under nitrogen at a temperature between −30°C. and −40°C. The reaction mixture was kept at this temperature with stirring for 2 hours, whereafter the temperature was allowed to rise gradually to −20°C. and 7.3 g of N-dimethyl chloroformamide in 20 ml of ether were added slowly, still under nitrogen. When addition of this ether solution was completed, the reaction mixture was allowed to reach gradually the room temperature and maintained in these conditions with stirring for 2 hours. The product which precipitated was filtered by suction, dried in vacuo to remove the last traces of ether and shaken with 30 ml of a mixture of 10 parts of water and 1 part of concentrated HCl. The orange-coloured oil which first separated solidified slowly to a yellow product which was filtered, washed with water until the washings were neutral and dried in a vacuum oven. There was thus obtained 15 g of product melting at 105—107°C. (Yield 73%).

The product crystallized first from benzene-petrol (1:3), then from ethanol-water (2:1). Melting point 114—115°C.; pale-yellow.

Analysis:

Calculated for $C_{28}H_{31}NO_4$: C 74.80 H 6.52 N 3.36
Found: C 74.68 H 6.32 N 3.24

EXAMPLE 5

1,1,2-tris-(*p*-methoxyphenyl)allyl alcohol

To a suspension of 24 g of lithium aluminium hydride in 1200 ml of anhydrous ether, a suspension of 28 g of tris-(*p*-methoxyphenyl)-acrylic acid in 1800 ml of dry ether was added slowly with stirring but without cooling. When addition of the acid was ended, the mixture was heated with stirring on a steam-bath under mild reflux of the ether for 6 hours, whereafter it was kept at room temperature for 12 hours while stirring of the mass was continued.

A mixture (1200 ml) obtained from 1080 ml of water and 120 ml of concentrated HCl was added with caution under refrigeration with freezing mixture. After a vigorous mechanical stirring, the ether layer was separated and the aqueous layer extracted a second time with ether. The ether extracts were combined, washed with water, dried over sodium sulphate

and filtered upon addition of a little decolorizing carbon. The ether was evaporated and the residual solid washed with petroleum ether. There was thus obtained 24 g of a white product melting at 111—113°C. (Yield 893%).

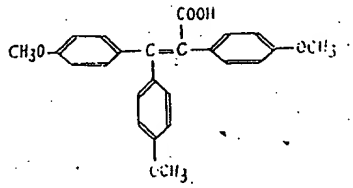
The product, recrystallized from a mixture of 1 part of benzene and 3 parts of petrol (b.p. 100—110°C.) had a melting point of 113°C.

Analysis:

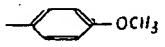
Calculated for $C_{24}H_{24}O_4$:	C 76.57	H 6.42
Found:	C 76.42	H 6.47

WHAT I CLAIM IS:—

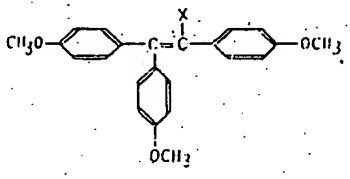
1. A method for the preparation of tris-(*p*-methoxyphenyl) ethylene derivatives possessing estrogenic properties, characterised by esterifying or reducing tris-(*p*-methoxyphenyl)-acrylic acid having the formula



or reacting a corresponding compound, wherein the carboxyl group is replaced by a bromine atom, with an alkyl lithium and N,N-dimethyl chloroformamide, without causing modification of the three *p*-methoxyphenyl groups.



and providing a product which may be represented by the general formula



wherein X represents a carboxylic acid ester, a dialkylamide or a hydroxymethyl group.

2. A method according to claim 1, wherein an ester with a saturated aliphatic alcohol with 1 to 4 carbon atoms is produced.

3. A method according to claim 2, wherein tris - (*p* - methoxyphenyl) - acrylic acid methyl ester is produced.

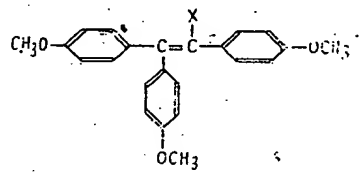
4. A method according to claim 2, wherein tris - (*p* - methoxyphenyl) - acrylic acid n-propyl ester is produced.

5. A method acording to claim 2, wherein tris - (*p* - methoxyphenyl) - acrylic acid n-butyl ester is produced.

6. A method according to claim 1, wherein tris - (*p* - methoxyphenyl) - acrylic acid N,N-dimethyl amide is produced.

7. A method according to claim 1, wherein 1,1,2 - tris - (*p* - methoxyphenyl) - allyl alcohol is produced.

8. A tris - (*p* - methoxyphenyl) ethylene derivative, produced by the method claimed in claim 1, which is represented by the formula:



wherein X represents a carboxylic acid ester, a dialkyl-amide or a hydroxymethyl group.

9. A compound according to claim 8, consisting of an ester with a saturated aliphatic alcohol having 1 to 4 carbon atoms.

10. A compound according to claim 9, consisting of the methyl ester of said acid.

11. A compound according to claim 9, consisting of the N-propyl ester of said acid.

12. A compound according to claim 9, consisting of the n-butyl ester of said acid.

13. A compound according to claim 8, consisting of the N,N-dimethyl amide of said acid.

14. A compound according to claim 8, consisting of 1,1,2-tris-(*p*-methoxyphenyl)-allyl alcohol.

15. A method for the preparation of tris-(*p*-methoxyphenyl) ethylene derivatives possessing estrogenic properties, as particularly described with reference to any of the examples herein, and derivatives produced in accordance therewith.

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